Claim Amendments:

Claim 1. (Currently amended) A solid pharmaceutical composition for oral administration comprising a benzofuran derivative with antiarrhythmic activity, or a pharmaceutically acceptable salt thereof, as an active principle, and a pharmaceutically acceptable nonionic hydrophilic surfactant optionally in combination with one or more pharmaceutical excipients, said nonionic hydrophilic surfactant being present in a proportion of from 1% to 50% by weight of the active principle in base form.

Claim 2. (Previously amended): A pharmaceutical composition according to Claim 4, wherein the benzofuran derivative is dronedarone hydrochloride.

Claim 3. (Previously amended): A pharmaceutical composition according to Claim 4, wherein the benzofuran derivative is amiodarone hydrochloride.

Claim 4. (Previously amended): A pharmaceutical composition according to Claim 14 wherein the pharmaceutically acceptable salt is the hydrochloride.

Claim 5. (Previously amended): A pharmaceutical composition according to Claim 1 wherein the nonionic hydrophilic surfactant is selected from the group consisting of poloxamers, polyethyoxylated castor oils, ethoxylated polysorbates and polyethylene hydroxystearates.

Claim 6. (Previously amended): A pharmaceutical composition according to Claim 5 wherein the nonionic hydrophilic surfactant is selected from the group consisting of poloxamer 124, poloxamer 188, poloxamer 237, poloxamer 338, poloxamer 407, polysorbate 20, polysorbate 40, polysorbate 60, polysorbate 80 and the products Cremophor® RH 40 and Solutol® HS15.

Claim 7. (Previously amended): A pharmaceutical composition according to Claim 15 wherein the nonionic hydrophilic surfactant is poloxamer 407.

Claim 8. (Cancelled)

Claim 9. (Currently amended): A pharmaceutical composition according to ~~Claim 8~~ Claim 6, in tablet or gelatin capsule form, wherein the nonionic hydrophilic surfactant is present in a proportion of from 1% to 20% by weight of the active principle in base form.

Claim 10. (Previously amended): A pharmaceutical composition according to Claim 9, in tablet or gelatin capsule form, wherein the nonionic hydrophilic surfactant is present in a proportion of from 5% to 15% by weight of the active principle in base form.

Claim 11. (Currently amended): A pharmaceutical composition according to ~~Claim 8~~ Claim 6 containing from 50 to 500 mg of active principle.

Claim 12. (Previously amended): A pharmaceutical composition according to Claim 11, in tablet or gelatin capsule form, containing from 200 to 400 mg of active principle.

Claim 13. (Previously amended): A pharmaceutical composition according to Claim 12, in tablet or gelatin capsule form, containing from 200 to 400 mg of active principle, calculated in base form, and 10% by weight of nonionic hydrophilic surfactant relative to the active principle in base form.

Claim 14. (Previously added): A pharmaceutical composition according to Claim 1 wherein the benzofuran derivative is selected from the group consisting of amiodarone and dronedarone or a pharmaceutically acceptable salt thereof.

Claim 15. (Previously added): A pharmaceutical composition according to Claim 6 wherein the benzofuran derivative is selected from the group consisting of amiodarone and dronedarone or a pharmaceutically acceptable salt thereof.

Claim 16. (Previously added): A pharmaceutical composition according to Claim 7 wherein the benzofuran derivative is dronedarone hydrochloride.

Claim 17. (Previously added): A pharmaceutical composition according to Claim 10 wherein the benzofuran derivative is selected from the group consisting of amiodarone and dronedarone or a pharmaceutically acceptable salt thereof.

Claim 18. (Previously added): A pharmaceutical composition according to Claim 17 wherein the nonionic hydrophilic surfactant is poloxamer 407.

Claim 19. (Previously added): A pharmaceutical composition according to Claim 18 wherein the benzofuran derivative is dronedarone hydrochloride.

Claim 20. (Currently amended): A pharmaceutical composition according to Claim 13 wherein the active principle is selected from the group consisting of amiodarone and dronedarone or a pharmaceutically acceptable salt thereof ~~and the nonionic hydrophilic surfactant is poloxamer 407~~.

Claim 21. (Previously added): A pharmaceutical composition according to claim 20 wherein the nonionic hydrophilic surfactant is poloxamer 407.

Claim 22. (Previously Amended): A pharmaceutical composition according to claim 21 wherein the active principle is dronedarone hydrochloride.

REMARKS

Claims 1-7 and 9-22 are in the application as amended.

Claim 1 is amended to incorporate the limitations of Claim 8, thereby more particularly defining the surfactant content of the composition. Claim 8 is accordingly cancelled.

Claims 9 and 11, previously dependent from Claim 8, are amended to depend from Claim 6.

Claim 20 is amended to delete therefrom the limitation recited in Claim 21.

No new matter is added by these amendments.

In the Office Acton mailed April 23, 2003 (Paper No. 13), the Examiner made final the rejection of Claims 1-22 previously made in Paper Nos. 8 and 11 over Martin-Algarra et al, Story et al, and the Physicians Desk Reference under 35 U.S.C. § 103(a) and 35 U.S.C. § 102(b).

It is the Examiner's position that the PDR teaches an oral formulation of amiodarone tablets and that amiodarone is slightly soluble in water; that Story et al teach a pharmaceutical delivery system of non-ionic hydrophilic surfactants for poorly water soluble active agents such as NSAIDs, and that Martin-Algarra et al teach compositions of amiodarone in a non-ionic hyrophilic surfactant such as polysorbate 80. The Examiner maintains that it would have been obvious to have administered amiodarone orally in a non-ionic hydrophilic surfactant composition since the PDR teaches that amiodarone is slightly soluble in water and the surfactant systems of Story et al demonstrate the solubilization of insoluble drugs such as NSAIDs, and because both the NSAIDs of Story et al and the antiarrhythmics of the instant application are known to be poorly water soluble. Motivation to formulate amiodarone and dronedarone in a hydrophilic anionic (sic. non-ionic) surfactant would come from the need for a rapidly absorbed orally available antiarrhythmic such as amiodarone. Additionally, absorption would be expected to be improved as taught by Martin-Algarra et al., thereby providing additional motivation.

The rejection is again respectfully traversed and reconsideration thereof is requested. As previously pointed out by Applicants, the PDR not only discloses that amiodarone is slightly soluble in water, as noted by the Examiner, but it also teaches that amiodarone is slowly and variably absorbed; that mean plasma concentrations include considerable individual variability, and that food significantly affects amiodarone absorption [e.g. it

increases the area under the plasma concentration-time curve (AUC) and the peak plasma concentration (C_{max}) by a factor of 2.3 and 3.8, respectively and decreases the time to peak plasma concentration (T_{max}) by 37%]. This, of course, is the very problem addressed by applicants' invention. The absorption profile of amiodarone was known at least as early as 1985 when it was first approved for use, and yet, despite the 1990 Story et al. patent and the 1995 Martin-Algarra publication, the disclosures of which the Examiner urges would have made the solution provided by the instant invention obvious, the 2001 PDR entry for amiodarone indicates that the absorption problem has not yet been solved. In other words, although the slow and variable absorption by amiodarone has been known for more than 15 years and the teachings of Story et al. have been available for more than 10 years, increasing the absorption of amiodarone and reducing its variability have until now remained long-felt but unmet needs even with the additional motivation purportedly provided more than 5 years ago by Martin-Algarra et al. Had the cited prior art made the instant invention obvious, as urged by the Examiner, it would seem that the absorption problem related to amiodarone would have been solved long ago. Hence, it is respectfully submitted that the cited references would not have suggested applicants' invention.

Moreover, the Story et al. disclosure is directed to the formulation of NSAIDs with surfactants to give micelle-forming compositions primarily intended to protect both the stomach and intestine. Such formulations are stated to contain drug and surfactant in a weight ratio (drug:surfactant) of from 1:5.7 to 1:50. Thus, the surfactant is present in a proportion of from 570% to 5000% relative to the drug whereas the instant claims specify that the surfactant is present in a proportion of from 1% to 50% by weight relative to the active principle. Clearly, there is nothing in Story et al. that would have suggested using such a small amount of non-ionic hydrophilic surfactant to both increase rate and reduce variability of absorption of either NSAIDs or amiodarone and dronedarone, a conclusion with which the Examiner expressed agreement in Paper No. 11. However, as discussed hereinbelow, the Examiner appears to rely on Martin-Algarra et al for such teaching.

It is urged by the Examiner that Martin-Algarra et al. teach oral administration of amiodarone with polysorbate 80; that the absorption rate constants of amiodarone decreased as the surfactant concentration increased, absorption being unusually fast at lower surfactant concentrations; that the concentration of 0.75 mg dissolved in 10 ml would be 7.5%, by weight of the active principle in base form; and that a solid dispersion is recited.

In fact, the Martin-Algarra reference discloses the use of an *in situ* rat gut technique in which a solution of polysorbate 80 containing amiodarone hydrochloride was perfused directly into the small intestine of the rat to study intestinal absorption of amiodarone. Clearly, this is not oral administration nor is it the administration, oral or otherwise, of a solid composition. Thus, the reference nowhere discloses either oral administration or a solid pharmaceutical composition for oral administration. The Examiner refers to a "solid dispersion" recited at page 6, column 2, of the reference. Actually, the language referred to states that

> "...the previously reported conclusions about the convenience of designing more reliable forms of amiodarone, containing a suitable dose of surfactant as a solid dispersion or similar preparation, have been entirely confirmed here."

No explanation or description of the "reported conclusions" is given nor is there any description of the composition or properties of a "solid dispersion", or of what might constitute a "suitable dose of surfactant", or of a method for the preparation of such a solid dispersion. Applicants make clear that a solid pharmaceutical composition refers essentially to a composition formed entirety of pulverulent solid ingredients which can be tabletted at room temperature comprising the active principle and the excipients, these ingredients being essentially in powder form, and that the so-called semi-solid pharmaceutical compositions formed of substances in pasty or waxy form when they are brought to moderate temperature (<70° C) do not form part of the invention (specification, page 1, lines 25-35). Clearly, nothing in Martin-Algarra discloses such "solid pharmaceutical composition".

The Examiner urges that Martin-Algarra et al set forth the best mode of carrying out their invention, and since the methods for tabletting solid formulations are well known, Martin-Algarra et al are clearly in possession of the invention. Respectfully, the Examiner has provided no evidence that Martin-Algarra et al invented anything; or that the best mode of carrying out any supposed invention was disclosed; or that Martin-Algarra et al are in possession of any solid dispersion formulation. In any event, regardless of what the Examiner surmises might be known by Martin-Algarra et al, the reference stands for what it discloses, and nowhere does it disclose any solid pharmaceutical composition for oral administration, let alone Applicants' formulation in which a nonionic hydrophilic surfactant is present in a proportion of from 1% to 50% by weight of the active principle.

As regards concentrations, the Examiner refers to pages 2 and 5 of Martin-Algarra et al and maintains that on page 2 the text states that the absorption experiments were carried

out using eight polysorbate 80 solutions containing amiodarone, and that page 5 teaches 0.75 of amiodarone dissolved in 10 ml of perfusion fluid which includes polysorbate 80, which translates to 7.5% by weight of the active principle in base form. More precisely, the reference, at page 2, discloses that the eight solutions used in the perfusion experiments had polysorbate 80 concentrations of 0.4, 0.8, 2, 4, 8, 20, 40, and 80 mM and contained 75 μg/ml of amiodarone hydrochloride, and at page 5, that the selected dose of amiodarone was 0.75 mg dissolved in 10 ml of perfusion fluids in which, as noted above, the polysorbate 80 concentrations ranged from 0.4 mM to 80 mM. The 0.75 mg of amiodarone hydrochloride (MW 681.8) corresponds to 0.71 mg of amiodarone base (MW 645.3), and 10 ml of 0.4 mM to 80 mM polysorbate 80 (ave. MW 1310) contains 5 to 1050 mg of polysorbate 80. Accordingly, in each 10 ml of perfusion fluid, polysorbate 80 was present in a proportion of 666% to 140,000% by weight of amiodarone hydrochloride or 704% to 147,887% by weight of amiodarone base. In Applicants' composition, on the other hand, the nonionic hydrophilic surfactant is present in a proportion of 1% to 50% by weight of the active principle. Thus, not only does Martin-Algarra et al fail to teach a solid composition, or the administration thereof, oral or otherwise, it fails to teach or suggest any composition, in any form, which contains a nonionic hydrophilic surfactant that is present in a proportion of from 1% to 50% by weight of the active principle. In fact, the reference specifies that the lowest concentration of surfactant tested [i.e., 0.4 mM (5 mg) or 704% relative to the active ingredient] is the concentration that "provides the minimal amount of surfactant leading to amiodarone solubilization" (page 5, column 1) and, therefore, actually teaches away from Applicants' invention which requires at least 700 times less surfactant to achieve solubilization and reduce absorption variability. Accordingly, it is submitted that the Martin-Algarra reference not only fails to either teach or suggest Applicants' claimed invention, it actually teaches away from it and is therefore incompetent to support the rejections based thereon.

As to the rejection for obviousness-type double patenting over U.S. Patent No. 6,143,778, the Examiner urges that the conflicting claims are not patentably distinct because both are drawn to a pharmaceutical composition of amiodarone and a non-ionic hydrophilic surfactant, and that although the amiodarone of the –778 patent is for parenteral administration, it would have been obvious to lyophilize the compositions of the patent and administer them orally. The rejection is again traversed and reconsideration thereof is requested.

The claims of the –778 patent are drawn to parenteral solutions containing amiodarone hydrochloride, a buffer solution capable of maintaining a pH of 2.4-3.8 and a

non-ionic hydrophilic surfactant. The role of the surfactant is to permit preparation of clear, stable, concentrated solutions of active principle which can be subsequently diluted for administration by perfusion. There is nothing in the reference to suggest lyophilizing the mixture of active agent, buffer and surfactant to prepare a solid oral preparation nor is there anything to suggest that oral administration of such a mixture would enhance the rate of absorption and reduce its variability. Thus there is nothing in the –778 patent that would render the instant claims obvious and hence the patent is not a proper basis for a double patenting rejection and the withdrawal thereof is respectfully requested.

In view of the foregoing, it is clear that Martin-Algarra et al discloses neither a solid pharmaceutical composition for oral administration nor any such composition containing a benzofuran derivative having antiarrhythmic activity in combination with nonionic hydrophilic surfactant which is present in a proportion of 1% to 50% by weight of the benzofuran derivative as here-claimed, and insofar as the reference is cited in support of a rejection of the instant claims under 35 U.S.C. § 102(b), such rejection is simply untenable and cannot stand.

Nor would Martin-Algarra et al have suggested Applicants' claimed composition. Nowhere does the reference suggest that the absorption of a benzofuran antiarrhythmic agent in any composition would be enhanced by a nonionic hydrophilic surfactant present in a proportion of 1% to 50% by weight of the active agent. In fact, the reference teaches that the minimum amount of surfactant required is at least 700-fold greater than the amount present in Applicants' composition. Story et al likewise teaches formulations containing surfactants in a proportion of at least 570% by weight relative to the active ingredient, i.e., at least 570-fold greater than the amount of surfactant in Applicants' compositions, and Story et al therefore adds nothing to Martin-Algarra et al. Thus, the Martin-Algarra et al and Story et al references, considered either individually or in combination, simply would not have suggested Applicants' compositions, and are therefore manifestly incompetent to support a rejection under 35 U.S.C. § 103(a).

Claims 1-7 and 9-22 are directed to solid pharmaceutical compositions for oral administration containing an antiarrhthmic benzofuran derivative and a nonionic hydrophilic surfactant in a proportion of from 1% to 50% by weight of the benzofuran derivative, which compositions solve the long-felt but unmet needs of increasing absorption and reducing variability. There is nothing in any of the cited references considered individually or in any

combination that would fairly teach or suggest such compositions, and accordingly, the rejections based thereon should be withdrawn.

There being no remaining issues, this application is believed in condition for favorable reconsideration an early allowance and such actions are earnestly solicited.

Respectfully submitted,

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